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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/597,604	06/20/2000	Joseph R. Moskal	97,186-D	6352

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 02/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/597,604	MOSKAL ET AL.
Examiner	**Art Unit**
Sumesh Kaushal Ph.D.	1636

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *5,6,9,10 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner. see PTO-948.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5&6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The instant application claims priority to a US App. Ser. No 08/969,437, filed 11/12/1997, now abandoned.

Election/Restrictions

Applicant's election with traverse of **Group II (Claims 1-4, 7-8 and 11-12)**, wherein the elected species is **α2,6-ST glycosyltransferase** in Paper No. 16 is acknowledged. The traversal is on the ground(s) that claims 1-4 links inventions I and II. The applicant argues that upon allowance of linking claims the restriction requirement as to the linked inventions shall be withdrawn. This is not found persuasive because there are no allowable generic or linking claim for the reasons as stated in rejections below.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-6, 9-10 and 13-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 16.

Claims 1-4, 7-8 and 11-12 are examined in this office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED.*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-4, 7-8 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use the invention**.

Nature Of Invention:

The present invention relates to the prevention and treatment of a disease by altering glycosyltransferase expression in a cell. Specifically the invention as claimed relates to the treatment a brain cancer by increasing the α2,6-ST glycosyltransferase activity.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses decreasing the tumorigenicity or malignancy of any and all type of brain cancers by altering the expression of any and all types of glycosyltransferases within brain cancer cells (in-vivo or in-vitro). In addition the scope of invention as claimed encompasses the modulation of any glycosyltransferase using any and all means (e.g. chemicals, proteins and nucleic acid molecules) including transfecting the target cells with an exogenous DNA encoding a glycosyltransferase. The specification as filed disclosed that all glioma specimen express α2,3-ST glycosyltransferase (fig-4, page 30 example-

1), whereas α2,6-ST glycosyltransferase expression was not observed in glioma or its metastases in brain. The specification further disclosed that lack of α2,6-ST glycosyltransferase in glioma cells leads to metastatic ability of glioma cells (page 34, lines 6-20). The specification disclosed the transfection of a human glioma cell line U373 MG with rat α2,6-ST cDNA using cationic liposomes, which resulted in the expression of α2,6-ST on cell surface (page 34, sec B). The specification further disclose that tranfection of nucleic acid encoding Gn-TV glycosyltransferase in glioma cells results in increase in tumor invasion by 4-10 folds an in-vitro assay, but fails to provide any evidence that transfection of nucleic acid encoding Gn-TV in a meningioma cell results in decrease in tumor invasion (page 11, lines 1-6). The specification further disclosed a nude mouse model to study the tumorigenicity of non-transfected (U-3T3MG) and transfected (α2,6-ST /U-3T3MG) glioma cells (page 46, example-4). The specification further disclosed that intra-cranial transplantation of α2,6-ST/U-3T3MG glioma cells in a mouse formed no tumors as compared to α2,3-ST/U-3T3MG transfectents and U-3T3MG control cells (page 48, line 4-14, fig-21). The specification further disclosed an adenoviral vector (Adα2,6-ST59) encoding α2,6-ST glycosyltransferase cDNA, wherein the cDNA is operatively linked to a CMV-promoter (page 57, sec A.). The specification further disclosed adenovirus mediate α2,6-ST glycosyltransferase gene expression in U-373MG glioma cell line in-vitro (page 59, sec B). In addition the specification proposed the use of Ad α2,6-ST59 in treating established tumors or in the prevention of brain tumors following surgical resection of tumor. However the disclosure falls short of providing any evidence that such a treatment would decrease the tumorigenicity and/or malignancy of any and all type of brain cancers in any animal (see page 60-62, example-8, 9).

State Of Art And Predictability:

The state of art at the time of filing was such that the expression and role of glycosylgransferases in the cancer development not only depends upon the type of organ but also depends upon the type of cancer in particular organ. For example, over expression of α2,6-ST glycosyltransferase has been suggested to play an important role in the oncogenic transformation of colon mucosa and is considered to be an indicator of metastatic and invasive potential in colon cancer. On the other hand human gliomas express very high levels α2,3-ST glycosyltransferase but lacks even α2,6-linked terminal sialic acids (Yamamoto et al Can. Res. 61;6822-6829, 2001, Yamamoto et al J Neurochem. 68: 2566-2576, 1997). Furthermore α2,6-ST glycosyltransferase mRNA, protein, and 2,6-linked sialic acids are expressed in meningiomas, chordomas, and craniopharyngiomas but no 2,6-ST expression was found in malignant gliomas or in medulloblastomas (Kaneko et al Acta Neuropathol 91:284-292, 1996) . Thus the state of the art clearly teaches that in brain cancer the role of each glycosyltransferase is distinct and is even specific to the tumor type of interest.

In addition, the treatment of a cancer is considered highly unpredictable because various genetic and etiological factors govern the development of the cancer. The carcinogenesis is a progressive disorganization and there is a loss of proliferation controls, increased aneusomy and heterogeneity which leaves limited reliable molecular targets for an intervention therapy (Kelloff et al, Eur. J. Cancer. 35(14):2031-2035, 1999, page 2032, col.2 para.3; page 2034, table-1). Furthermore, the tumors are heterogeneous in respect that they differ in genetic mutations, expression of oncogenes, immunogeneicity and response to environmental changes. The cancer therapy clearly demands molecular, phenotypic and functional characterization of a particular

tumor type that proves amenable to induce cancer amelioration in vivo. (Gomez-Navarro et al, Eur. J. Cancer. 35(6);867-885, 1999, page 868, table-1). Furthermore, the malignant gliomas remains poorly understood form of cancer. The state of art clearly suggests that future treatment strategies will likely involve synergistic combinations of agents aimed at different pathways in the molecular pathogenesis of this type of cancer (Avgeropoulos et al The Oncologist 4:209-2224, 1999, page 220 col.2)

Furthermore, invention as claimed requires genetic manipulation of cancer cells in a subject. The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. For example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Touchette, page 7 col.3, para.1; Anderson page 29 col.1, para.6). Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any

apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3). In instant case the specification fails to disclose that increase of activity of α2.6-ST glycosyltransferase would decrease the tumorigenicity and/or malignancy of any and all type of brain cancers in any animal. Furthermore considering the fact that the treatment of malignant gliomas is highly unpredictable (see Avgeropoulos et al The Oncologist 4:209-2224, 1999) the specification fails to provide a single working example wherein the administration of vector encoding the α2.6-ST glycosyltransferase results in decrease the tumorigenicity and/or malignancy of an established glioma in any animal.

In addition, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1).

Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). Considering the applicants disclosure the in-vitro transduction of a tumor cell line does not correlate to therapeutic delivery of α2.6-ST DNA in-vivo. Furthermore, the transplantation of previously transfected U373 MG/α2.6-ST cells in a mouse does not correlate to the invention as claimed because the method requires the transduction of therapeutic genes (glycosyltransferases) into brain cancer cells and not the transplantation of previously transfected cells which would have no effect on the brain cancer cells already present in an individual. The state of the art clearly suggests that although the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals

Quantity Of Experimentation Required:

In instant case decreasing the tumorigenicity or malignancy of any and all type of brain cancer by altering the expression of glycosylation of any protein by altering the activity of any glycosyltransferase with in the cancer cell via any and all means is not considered routine in the art and without sufficient guidance how to modulate the activity of a spcific glycosyltrasferase in context to a specific brain cancer type the experimentation left to those skilled in the art is

unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Furthermore, it is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Therefore, considering the unpredictability in the state of art and limited guidance provide in the specification one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation requires would include the evaluation of any and all agents encompassing chemicals, proteins and DNA molecules that alters the activity (increase or decrease) of any and all glycosysltransferases resulting in decrease in tumorigeneicity or malignancy of a brain cancer. The undue experimentation requires would further include the evaluation of the role of each known glycosyltransferase in a specific brain cancer type. In addition, undue experimentation required would include the administration of any and all types of viral and non-viral vectors via

any and all routes of administration (systemic or direct tumor injection) and evaluation of therapeutic efficacy.

2. Claims 1-4, 7-8 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention**.

The invention as claimed encompass a method for decreasing the tumorigenicity or malignancy of brain cancer cell comprising increasing the activity of any glycosyltransferase of any brain cancer cell type using any and all means. The scope of invention as claimed encompasses increasing the claimed glycosyltransferase activity by administering an exogenous protein, a chemical agent that modulates the bioactivity or transcriptional regulation of glycosyltransferases synthesis, and a genetic vector encoding the glycosyltransferases activity to a brain cancer cell in vivo. In addition the invention as claimed (claims 11-12) encompass increasing glycosyltransferase activity by stable transfection of an exogenous DNA encoding a glycosyltransferase expressibly linked to an inducible promoter. At best the specification only disclosed the transfection of a human glioma cell line U-373MG with a recombinant adenoviral vector comprising nucleic acid encoding α2,6-ST under transcriptional control of human CMV promoter (page 59, sec B). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs

Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In instant case the specification fails to disclose a method of increasing glycosyltransferase activity (as claimed) by administering any exogenous protein or any chemical agent that increase the bioactivity or increase the transcriptional regulation of a specific glycosyltransferases synthesis. Furthermore the specification fails to disclose a single inducible promoter that regulates the glycosyltransferases gene expression. Considering the applicant's disclosure it is even unclear what is the agent used to regulate the expression of the inducible promoter as claimed. Thus, one skill in the art would conclude that applicant was not in the possession of the all the method for decreasing the tumorigenicity or malignancy of brain cancer cell, which comprises altering the activity of a glycosyltransferase of the cell by any and all means.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 7-8 are indefinite because instant claims recites limitation altering/increasing the activity of a glycosyltransferase. It is unclear how the glycosyltransferase activity is altered or increased in this context. Alteration or increasing the activity of a glycosyltransferase is 'the result" and not "the step". It is unclear what does a practitioner need do to alter or increase the claimed glycosyltransferase activity in this context.

Claim 1 recites the limitation "said altered pattern" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 7 recites the limitation "said altered activity" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "said altered activity" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al (Proc Annu Meet Am Assoc Cancer Res, 37:63, A436 March 1996). The cited art teaches a method of decreasing tumor invasivity of human glioma cell in-vitro. The cited art further teaches that α2,6 sialyltransferase (α2,6-ST) gene transfection alters the integrin-mediated invasivity of the human glioma cell line U-373MG. The cited art further teaches that transfected glioma cells express α2,6-ST and α2,6-linked sialogycoprotein on their surface and show marked reduction in α3β1 integrin-mediated adhesion to the extra cellular matrix proteins, and tumor cell invasiveness in-vitro as compared to untransfected controls. The cited art concluded that changes in the terminal sialylation have marked effect on α3β1 integrin-mediated glioma invasivity and suggested the use of this approach to alter invasivity of glioma cells by

glycosyltransferase gene transfection (page 63 col.1 abstract #436). Given the broadest reasonable interpretation the invention as claimed encompasses a method of decreasing the tumorigenicity or malignancy of brain cancer cell in-vitro, thus the cited art clearly anticipate the invention as claimed.

Claim Objections

Claim 1 is objected to because of the following informalities: claim 1 in line 3-4 recites limtation "activity of glycosyltransferase". Amendment of instant claim to reads upon "activity of a glycosyltransferase" would obviate this rejection.

Claims 2-4, 7-8 and 11-12 are objected to because of the following informalities: In instant case, dependent claims 2-4, 7-8 and 11-12 recite "A method" in line 1. Amendment of instant claims to read upon "The method" in place of "A method" would obviate this rejection. Appropriate correction is required.

Claims 8 and 12 are objected to because it contains non-elected species of glycosyltransferase, which do not encompasses the elected subject matter (α2,6-ST glycosyltransferase).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be

proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER